REMARKS

INTRODUCTION:

In accordance with the foregoing, independent claims 1, 10 and 19 have been amended to refer to an "acetone-free" process and an "ethanol-free" aqueous solution and to the ratio of isopropyl alcohol to methanol in the mixture of isopropyl alcohol, methanol and water, as discussed below. In addition, dependent claims 2-9, 11-12, 15-18 and 20 are amended for better form and/or clarity, change dependencies, and to correct a typographical error in the structure of Gabalactam in claim 10. See, for example, page 3, lines 15-18 of the application as filed for support. Furthermore, new independent claims 21-23 have been added. Support for new claims 21-23 may be found, for example, on page 10, lines 9-11; page 13, line 9, to page 14, line 4; and on page 16, lines 9-14, of the specification as filed; and in claims 1 and 10 as originally filed.

Independent claims 1, 19, 21 and 23 are directed toward the preparation of Gabapentin, and independent claims 10 and 22 are directed toward the preparation of Gabalactam.

Claims 1-12 and 14-23 are pending and under consideration. Reconsideration is respectfully requested.

REJECTION UNDER 35 U.S.C. §112:

Claims 1-12 and 14-20 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. This rejection is traversed and reconsideration is requested.

With this Amendment, amended independent claims 1, 10 and 19 now recite, in part: "a mixture of isopropyl alcohol, methanol and water in a ratio ranging from 4.54-19.64 : 3.88-15.64 : 1 (v/v), wherein the ratio of isopropyl alcohol to methanol is in the range from 0.58 : 1 to 1.32 :1 (v/v) ... ." The support may be found, for instance, by the description of Examples 1 to 10 in the specification.

According to MPEP §2163.05, Section III "Range Limitations," relying on *Union Oil of Cal. v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 USPQ2d 1227, 1232-33 (Fed. Cir. 2000), "Description in terms of ranges of chemical properties which work in combination with ranges of other chemical properties to produce an automotive gasoline that reduces emissions was found

to provide an adequate written description even though the exact chemical components of each combination were not disclosed and the specification did not disclose any distinct embodiments corresponding to any claim at issue. '[T]he Patent Act and this court's case law require only sufficient description to show one of skill in the . . . art that the inventor possessed the claimed invention at the time of filing.' "

Similarly, the ten examples in the specification contain subject matter that is described in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The ratios stated in the amended claim language of "a ratio ranging from 4.54-19.64:3.88-15.64:1 (v/v), wherein the ratio of isopropyl alcohol to methanol is the range from 0.58 : 1 to 1.32 : 1" recite the ranges covered by the Examples 1-10 on pages 17-23 of the application as filed, and are summarized in the table below:

Example No.	ml of isopropyl alcohol (IPA)	ml of methanol	ml of water (H_20)	IPA:Methanol:H_20	IPA:Methanol
1	815	80+570 = 650	16+60= 76	10.72 : 8.55 : 1	1.25 : 1
2	275	27+192= 219	3+11= 14	**19.64 : 15.64 : 1**	1.26 : 1
3	174	20+145= 165	6+23= 29	6 : 5.68 : 1	1.06 : 1
4	360	33+240= 273	8+30= 38	9.47 : 7.18 : 1	**1.32 : 1**
5	116	25+174= 199	5+20= 25	4.64 : 7.96 : 1	**0.58 : 1**
6	360	50+360= 410	5.5+21= 26.5	13.58 : 15.47 : 1	0.88 : 1
7	500	86+625= 711	13+50= 63	7.93 : 11.28 : 1	0.70 : 1
8	260	3.6+260= 263.6	9+36= 45	5.77 : 5.85 : 1	0.99 : 1
9	370	52+370= 422	12+45= 57	6.49 : 7.40 : 1	0.88 : 1
10	600	63+450= 513	27+105= 132	**4.54 : 3.88 : 1**	1.17 : 1

As noted in the above-quoted Section III of MPEP §2163.05, because there is a description in terms of ranges of the chemicals used for recrystallizing the precipitate in the present application, the phrase "a ratio ranging from 4.54-19.64:3.88-15.64:1 (v/v), wherein the

ratio of isopropyl alcohol to methanol is in the range from 0.58 : 1 to 1.32 : 1 (v/v)" in amended independent claims 1, 10 and 19 is supported. Particularly, Examples 10 and 1 in the specification provide the range of isopropyl alcohol as "4.54-19.64," and the range of methanol as "3.88-15.64." In addition, as to the ratio of isopropyl alcohol to methanol, Example 5 provides the lower limit of the range at 0.58 : 1, and Example 4 provides the upper limit of the range at 1.32 : 1. Also, because, as described by Applicants in the specification at pages 10, line 27 to page 13, line 4 of the Application as filed, different crystallizing chemicals and/or different mixtures of chemicals were needed for the Gabapentin purification as required in the pharmaceutical field.

Thus, because the amended recitations are contained in the examples of the specification of the original application, they cannot constitute new matter. Also the specified ratios of "4.54 – 19.64 : 3.88 – 15.64 : 1 (v/v), wherein the ratio of isopropyl alcohol to methanol is in the range of 0.58 : 1 to 1.32 : 1" are clearly taught by the original specification.

Hence, claims 1-12 and 14-20 are believed to fully comply with 35 U.S.C. §112.

REJECTION UNDER 35 U.S.C. §103 AND EXAMINER'S RESPONSE TO ARGUMENTS:

Claims 1-12 and 14-20 were rejected as being made obvious by Peverali et al. (USPN 6,518,456; hereafter, **Peverali**) in view of Cannata et al. (US Patent Publication 2004/0068011; hereafter, **Cannata**). The rejection is traversed and reconsideration is requested.

Independent claims 1 and 19 have been amended to recite, in part: "An acetone-free process for the preparation of Gabapentin." Independent claim 10 has been amended to recite, in part: "An acetone-free process for the preparation of Gabalactam."

It is clear to one skilled in the art that none of Examples 1-10 in the written description utilizes acetone in the process of the present invention. Hence, the use of acetone in the purification of Gabapentin is not part of the invention recited by these claims. In contrast, **Peverali** teaches "washing the filter with acetone" (**Peverali**, column 3, lines 4-5) and "digestion of gabapentin hydrochloride in acetone" (**Peverali**, column 3, line 36). Thus, amended claims 1, 10 and 19 are patentably distinguishable over **Peverali**.

Independent claims 1, 10 and 19 have also been amended to recite, in part:

"preparing an ethanol-free aqueous solution of Gabapentin hydrochloride."

It is clear to one skilled in the art that none of Examples 1-10 in the written description utilizes ethanol in the process of the present invention. Hence, with respect to amended independent claims 1 and 19, which are directed toward the preparation of Gabapentin, the use of ethanol in the purification of Gabapentin is not part of the invention according to amended claims 1 and 19. With respect to amended independent claim 10, which is directed toward the preparation of Gabalactam, because the first step in such process involves preparing an ethanol-free aqueous solution of Gabapentin, the use of ethanol in the purification is also not part of the invention according to amended claim 10. In contrast, **Peverali** teaches digestion involving ethanol (**Peverali**, Abstract, lines 6-7), and washing involving an ethanol/water mixture (**Peverali**, column 2, lines 34-35). Therefore, amended claims 1, 10 and 19 herein are not obvious over **Peverali** as one having ordinary skill in the art would not have been prompted by the teachings of **Peverali** to arrive at the invention according to these claims. There is no suggestion in **Peverali** that acetone and ethanol should be omitted.

In addition, the Examiner admits: "**Peverali** et al. is deficient in the sense that it does not teach recrystallization of the precipitate from a mixture of isopropyl alcohol, methanol and water."

However, the Examiner further argues: "**Cannata** et al. teaches the purification and recrystallization of gabapentin with isopropyl alcohol, methanol and water (see Cannata, page 2, Paragraph [0028])." Applicants respectfully disagree because **Cannata** does not teach the use of water in conjunction with isopropyl alcohol and methanol.

Cannata, at page 2, paragraph [0028] recites:

> [0028] Methanol (95 Kg) was added to the residue in four portions and the mixture was heated with water thermoregulated in jacket at 55-60° C. for about 1 hour. Isopropylic alcohol (395 Kg) was added to the obtained homogeneous suspension in about 20/30 minutes, with circulation of water thermoregulated at 60-65° C. At the end of the addition, the mixture was kept under stirring for about 30/60 minutes, always with circulating water thermoregulated at about internal temperature 55° C., and then it was cooled first with water and then with saline solution at internal temperature about -5° C. After keeping at this temperature for at least 1 hour, centrifugating and washing with isopropyl alcohol, about 130-140 Kg of wet product were obtained which were dried under vacuum at 50-55°C. for about 24 hours obtaining about 120-130 Kg of gabapentin. (emphasis added)

As is clear from the above, water is not added to methanol and isopropyl alcohol in the **Cannata** method. Instead, water was only used to circulate in the jacket for thermoregulation without being part of the reaction solution. Therefore, **Cannata** does not teach or suggest a

mixture of isopropyl alcohol, methanol and water for recrystallizing the precipitate as recited in amended claims 1, 10 and 19.

Furthermore, as recited in amended claims 1, 10 and 19, the mixture used for recrystallization contains isopropyl alcohol, methanol and water in a ratio ranging from 4.54 – 19.64 : 3.88 – 15.64 : 1 (v/v). The amount of water in the mixture can be calculated in the following way:

(A) When the recrystallization mixture is in the ratio of 4.54 : 3.88 : 1, the percentage of water is:

$$[1 \div (4.54 + 3.88 + 1)] \times 100\ \% = [1 \div 9.42] \times 100\ \% = 10.62\ \%;$$

(B) When the recrystallization mixture is in the ratio of 19.64 : 15:64 : 1, the percentage of water is:

$$[1 \div (19.64 + 15.64 + 1)] \times 100\ \% = [1 \div 36.28] \times 100\ \% = 2.75\ \%.$$

Therefore, according to amended claims 1, 10 and 19, the amount of water in recrystallization is in the range of 10.62 % to 2.75 %.

The Examiner has submitted three specification sheets from Sigma-Aldrich: 190764 for 2-Propanol, 179957 for Methanol, and 667390 for Methanol Solution. Specification 190764 provides that the 2-propanol contains less than or equal to 0.2% water. Similarly, Specification 179957 provides that the methanol is in a form that includes less than or equal to 0.1% water. It is clear that the amounts of water as impurities in isopropyl alcohol and methanol are less than the amount of water ranging from 10.62 % to 2.75 % that is present in the isopropyl alcohol, methanol and water mixture in a ratio of 4.54-19.64 : 3.88-15.64 : 1 (v/v) recited in amended claims 1, 10 and 19. Hence, it is not reasonable to expect that water would be present in the alcohol solutions in the amounts utilized in the present application, which appears to be the position that is submitted by the Examiner.

The specification sheet 667390 of Sigma-Aldrich provides a special use methanol solution containing 0.1 % (v/v) trifluoroacetic acid and 5 % (v/v) water. This methanol solution is for High Performance Liquid Chromatography (HPLC) in which the methanol is used in a mobile phase wherein, in the chromatography, as an analyte traverses the column, the sample components become distributed according to their relative affinity for the mobile and the stationary phases. Such a special use of the methanol solution for HPLC is not likely to be utilized in recrystallization of Gabapentin such as with the present invention because, for instance, the 0.1 % of trifluoroacetic acid in the methanol solution for HPLC will introduce an

acidic species again to Gabapentin, leading to possibly a species such as Gabapentin hydrogen trifluoroacetate. Hence, the specification sheet 667390 of Sigma-Aldrich refers to a methanol solution containing 0.1 % (v/v) trifluoroacetic acid and 5 % (v/v) water that is not applicable to the present invention according to amended independent claims 1, 10 and 19.

Therefore, amended claims 1, 10 and 19 of the application are not obvious over **Peverali** and **Cannata**, alone or in combination, because one having ordinary skill in the art would not have arrived at the invention based on the teachings of **Peverali** and **Cannata**. The lack of teaching in **Cannata** with respect to using water in the recrystallization mixture would not have prompted the modification of **Peverali** to use a "mixture of isopropyl alcohol, methanol and water."

To date, no one has been able to provide the high purity of Gabapentin obtained in an acetone-free process using isopropyl alcohol, methanol and water, as is recited in claims 1, 10 and 19. Hence, the results of the present invention are unexpected, and are not simply a variation of known solvent ratios or the like. The embodiments of the present invention provide a valuable method for purification of Gabapentin of a pharmaceutical purity as well as an efficient recovery method of Gabalactam, which can be utilized to prepare Gabapentin hydrochloride (page 24, lines 8-21 of the application as filed).

Affidavit of Kuppuswamy Nagarajan under Rule 1.132

To further support a conclusion of non-obviousness, attached hereto is a Rule 1.132 Affidavit (7 pages) of Kuppuswamy Nagarajan ("**Affidavit**"), a co-inventor of the present application. Also attached is the Biographical Data (5 pages) of Kuppuswamy Nagarajan, which is referred to in Paragraph 2 of the **Affidavit**. This **Affidavit** is submitted as evidence of non-obviousness under the guidelines of Graham v. John Deere Co., 383 U.S. 1, 148 U.S.P.Q. 459 (Sup. Ct. 1966). The Court of Appeals for the Federal Circuit has consistently held that such Declaration evidence should be fully considered. See, e.g., In re Wright, 193 U.S.P.Q. 332 (Fed. Cir. 1977); In re Fenn, 208 U.S.P.Q. 470, 473 (Fed. Cir. 1980) and In re Alton, 37 U.S.P.Q. 2d 1578 (Fed. Cir. 1996). Of course, the secondary considerations of Graham survived the relatively recent KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 82 U.S.P.Q.2d 1385 (2007). See, e.g., In re Sullivan, 84 U.S.P.Q.2d 1034 (Fed. Cir. 2007).

Kuppuswamy Nagarajan, in Paragraph 2 of the **Affidavit**, provides his credentials to support the conclusion that he is at least one of ordinary skill in this art. Paragraph 3 (page 1)

through Paragraph 7 (page 3) of the **Affidavit** show that Kuppuswamy Nagarajan is familiar with the invention and the background of the invention. In Paragraphs 8 through 10 (page 3) of the **Affidavit**, Kuppuswamy Nagarajan indicates that the inventors of this application unexpectedly found that, by using a combination of isopropyl alcohol, methanol and water as the solvent system for recrystallization, Gabapentin was obtained in high purity, meeting all the requirements of the pharmaceutical industry. Examples of the requirements include: less than 100 ppm in chloride content as impurity, less than 0.1 % Gabalactam content as impurity, and 40 – 60% yield of Gabapentin (see **Affidavit**, page 2).

In Paragraph 11 (page 3) of the **Affidavit**, Kuppuswamy Nagarajan summarizes the three major points:

(A) Gabapentin that is obtained from the aforementioned recrystallization solvent meets the requirements of the pharmaceutical industry.

(B) Gabapentin obtained from a recrystallization mixture that only contains methanol and isopropyl alcohol, each having only 0.1 % moisture, has a chloride content that exceeds the requirements of the of the pharmaceutical industry.

(C) Gabapentin obtained from a recrystallization mixture that contains a larger amount of water results in lower yield of the final product.

Kuppuswamy Nagarajan uses four separate experiments to arrive at the aforementioned three major points.

Experiment 1 (**Affidavit**, page 4) uses isopropyl alcohol (99.63 ml), methanol (73.1 + 5.96 = 79.06 ml) and water (7.69 + 0.27 = 7.96 ml) as the recrystallization solvent system. The ratio of the three solvents can be expressed as: (a) for isopropyl alcohol: (99.63 ÷ 7.96) = 12.52; (b) for methanol: (79.06 ÷ 7.69) = 9.93; and (c) for water, (7.69 ÷ 7.69) = 1. Therefore, the ratio of the isopropyl alcohol, methanol and water is "12.52 : 9.93 : 1," which is within the range recited in independent claims 1, 10 and 19. Consequently, Gabapentin obtained from such a mixture of solvent system shows 58 % yield, 0.007 % Gabalactam content, and 90 ppm chloride content, thus meeting the requirements of the pharmaceutical industry.

Experiment 2 (**Affidavit**, page 5) uses excessive amount of water by having isopropyl alcohol (99.63 ml), methanol (73.1+ 5.96 = 79.06 ml) and water (46.48 + 0.27 = 46.75 ml) as the recrystallization solvent system. The ratio of the three solvents can be expressed as: (a) for isopropyl alcohol: (99.63 ÷ 46.75) = 2.13; (b) for methanol: (79.06 ÷ 46.75) = 1.69; and (c) for water: (46.75 ÷ 46.75) = 1. The ratio of isopropyl alcohol, methanol and water is "2.13 : 1.69 : 1,"

which is NOT within the range recited in the independent claims 1, 10 and 19. Consequently, Gabapentin obtained from such a mixture shows 23.4 % yield, 0.004 % Gabalactam content, and 25 ppm chloride content, thus NOT meeting requirements of the pharmaceutical industry.

Experiment 3 (**Affidavit**, pages 5-6) uses no water by having isopropyl alcohol (99.63 ml) and methanol (73.1 + 5.9 = 79.0 ml) as the recrystallization solvent system. Without water, the ratio in this experiment is NOT within the range recited in the independent claims 1, 10 and 19. Consequently, Gabapentin obtained from this experiment shows 44.8 % yield, 0.006 % Gabalactam content, and 1,200 ppm chloride content, thus NOT meeting requirements of the pharmaceutical industry.

Experiment 4 (**Affidavit**, page 6) uses no water but more isopropyl alcohol (179.68 ml) and methanol (143 + 6.0 = 149.0 ml) as the recrystallization solvent system. Without water, the ratio in this experiment is NOT within the range recited in the independent claims 1, 10 and 19. Gabapentin obtained from this experiment shows 63% yield, 0.002 % Gabalactam content, but 1,000 ppm chloride content, thus NOT meeting requirements of the pharmaceutical industry.

Therefore, the **Affidavit** supports the use of isopropyl alcohol, methanol and water in the ratio of "4.54 – 19.64 : 3.88 – 15.64 : 1 (v/v)" as a recrystallization system for the preparation of Gabapentin is not obvious to one having ordinary skill in the art.

In addition, because Gabalactam is obtained from a mother liquor that uses the same mixture of isopropyl alcohol, methanol and water that produces Gabapentin, the **Affidavit** also supports the preparation of Gabalactam as not obvious to one having ordinary skill in the art.

Hence, amended independent claims 1, 10 and 19 are patentable under 35 U.S.C. §103(a) over **Peverali** in view of **Cannata**, alone or in combination. Since claims 2-9 depend from amended independent claim 1, claims 11-12 and 14-18 from amended independent claim 10, and claim 20 from amended independent claim 19, dependent claims 2-9, 11-12,14-18, and 20 are patentable under 35 U.S.C. §103(a) over **Peverali** in view of **Cannata** et al, alone or in combination, for at least the reasons stated above that amended independent claims 1, 10 and 19 are patentable under 35 U.S.C. §103(a) over **Peverali** in view of **Cannata** alone or in combination.

Furthermore, newly added claims 21-23 are not obvious over **Peverali** in view of **Cannata**.

New claims 21 and 23 are directed to a preparation of Gabapentin in a yield of over 50%. As can be seen in the attached **Affidavit** of Kuppuswamy Nagarajan, by recrystallizing

Gabapentin with isopropyl alcohol and methanol only, one obtains a yield of 44.8% (see **Affidavit**, pages 5-6, paragraph 15). In contrast, claims 21 and 23 require that a yield of over 50% be obtained. This solves one of the deficiencies of the prior art – low yield of Gabapentin.

New claim 22 is directed to a preparation of Gabalactam such that Gabalactam is obtained from the mother liquor that produces Gabapentin in a yield of over 50%.

The Federal Circuit's predecessor, the CCPA, had found that a purified form of an old product, and methods of making that form, are not obvious over the prior art if one of skill in the art would not know that such a purified form could exist or how it could be produced. In re Cofer, 354 F.2d 664, 668 (CCPA 1966). See also MPEP § 2144.04(VII). The same rationale applies here – one of skill in the art would not have recognized that Gabapentin could be produced in a yield of greater than 50% using the claimed process. Thus, new claims 21-23 are patentable under 35 U.S.C. §103(a) over **Peverali** in view of **Cannata**, alone or in combination.

CONCLUSION:

In accordance with the foregoing, it is respectfully submitted that all outstanding objections and rejections have been overcome and/or rendered moot. And further, that all pending claims patentably distinguish over the prior art. Thus, there being no further outstanding objections or rejections, the application is submitted as being in condition for allowance which action is earnestly solicited.

If the Examiner has any remaining issues to be addressed, it is believed that prosecution can be expedited by the Examiner contacting the undersigned attorney for a telephone interview to discuss resolution of such issues.

If there are any underpayments or overpayments of fees associated with the filing of this Amendment, please charge and/or credit the same to our Deposit Account No. 19-3935.

Respectfully submitted,

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